

REMARKS

In response to the Office Action mailed August 28, 2007, Applicant has canceled claims 10-26. New claims 27-52 have been added. It is urged that support for all the above amendments may be found throughout the specification as originally filed, specifically on page 8, lines 20-25; page 9, lines 20-22, and Figures 2B and 6. No new matter has been added. The above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the amendments, claims 27-52 are pending in the application. Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks.

Amendments

Applicant respectfully adds the negative limitation of a non-polynucleic acid-based cytotoxic or anti-neoplastic agent to the new claims. The claims examined in the Office Action of April 10, 2006 contained similar limitations and were held to satisfy the requirements of §112 as evidenced by the acceptance of these limitations by the Examiner. The negative proviso is added as per *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). Applicant submits that the entire new claim set is fully supported by the as-filed specification and does not constitute new matter.

Rejection under 35 U.S.C. §102(e)/§103(a), first rejection

Claims 10, 11, 15, and 16 stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as obvious over Falk *et al.* (U.S. 5,985,850). Specifically, the Examiner contends that Falk *et al.* teach a method of administration of anti-cancer or chemotherapeutic agent in combination with hyaluronic acid (HA) having a preferred molecular weight of ≤ 750 kilodaltons (kD). Applicant notes that

claims 10-26 have been canceled, and thus, the Examiner's rejection is rendered moot with regard to claims 10, 11, 15, and 16. However, Applicant will respond in full to the Examiner's arguments.

Applicant respectfully traverses these bases for rejection and submits that Falk *et al.* do not teach every limitation of the presently claimed invention, and thus, is not a proper anticipatory reference.

Applicant notes that the Examiner has previously agreed that "Falk *et al.* does not explicitly state that efficacy of a drug for a cancer cell is enhanced by administering a composition containing HA and anti-neoplastic or cytotoxic agent". Further, Applicant submits Falk *et al.* teach the use of HA exclusively to enhance the penetration and transport of the "agent" through the tissue surrounding the various cellular elements of a tumor by altering the penetration characteristics of the surrounding tissue (see col.2, lines 37-42 and lines 61-67; col. 10, lines 39-43; col. 11, lines 24-28 and lines 58-65; col. 12, lines 27-34; col. 13, lines 1-4, lines 29-35, and lines 61-67). Furthermore, Falk *et al.* explicitly postulate that the "HA and/or salts thereof ... facilitate the transport of the agent to the site to be treated and to penetrate the tissue (including scar tissue) through all membranes in the individual cells to be treated" (col. 14, lines 1-6). In contrast, the Applicant claims methods directed to enhancing the efficacy of a non-polynucleic acid-based cytotoxic or anti-neoplastic agent, and also methods to overcome acquired resistance of cancer cells to a non-polynucleic acid-based cytotoxic or anti-neoplastic agent by administering a specific range of molecular weight HA in combination with said agent. Applicant submits that Falk *et al.* do not claim the same methods as Applicant, and thus, do not anticipate the presently claimed methods.

Applicant submits that Falk *et al.* do not teach a composition of non-polynucleic acid-based cytotoxic or anti-neoplastic agent and HA, wherein the molecular weight of HA is: i) greater than 400kD (claim 2, support in Fig. 2B and Fig. 6; p.8, lines 20-25; p. 17, line 37; p. 29, line 28; p. 39, line 31; and p. 40, line 16 p.79, line 35; p. 80, line 4, and p. 81, Table 4); ii) 400-900kD (claim 3, support in Fig. 2B and Fig. 6; p.8, lines 20-25; p. 17, line 37; p. 29, line 28; p. 39, line 31; and p. 40, line 16 p.79, line 35; p. 80, line 4, and p. 81, Table 4); iii) 890kD (claim 5, support in Fig. 6; p. 17, line 37; and p. 29, line 28); and iv) 750kD (claim 6, support in p.79, line 35; p. 80, line 4, and p. 81, Table 4). Thus, as Falk *et al.* do not claim the same ranges of

molecular weights for HA as Applicant, Applicant's composition would inherently possess the surprising and unexpected properties imparted to high molecular weight HA, such as increasing the efficacy of a drug in treating a cancer cell, overcoming acquired drug resistance in a cancer cell, and an increased viscosity over lower molecular weight HA. In contrast, Falk *et al.*'s lower molecular weight HA compositions would possess decreased viscosity, which is essential for Falk *et al.*'s intended use of HA, and lack the unexpected properties of Applicant's composition. Moreover, it is impossible to identify any particular molecular weight for the HA used in the compositions for the 40 case studies described in Falk *et al.*, except for a single case that discloses a known HA formulation (see case study 37).

Accordingly, Falk *et al.* do not teach every limitation of the claims, and thus, do not anticipate the presently claimed methods.

In regard to the alternative §103 rejection over Falk *et al.*, the Examiner asserts that Falk *et al.* teach "the preferred" molecular weight for HA is less than 750kD. Applicants strongly contend that this is not an accurate representation of what Falk *et al.* consider to be "the preferred" molecular weight of HA. Although Falk *et al.* claim a range of HA from 150kD to 750kD, within this range, Falk *et al.* **explicitly teach** that "the preferred" molecular weight of HA is within the range of 150kD to 225kD as stated in col. 17, lines 36-42; col. 17, lines 51-59; and col. 18, lines 8-10. In no instance do Falk *et al.* recite that the entire range of molecular weights of HA ≤ 750 kD are "preferred". Applicant submits that the range of 150-225kD would be consistent with an increased mobility of the HA molecules (low viscosity) through tissues and membranes, which is Falk *et al.*'s postulated function for HA (col. 14, lines 1-6). Thus, the inherent properties of Falk *et al.*'s composition would not be expected to increase drug efficacy or overcome any acquired resistance to a drug as these novel properties are associated with higher molecular weight HA.

Further, the Examiner alleges that because there is no data to support that HA of different molecular weights influences the efficacy of a drug for a cancer cell line, it would be expected that Falk *et al.*'s composition containing HA and anti-cancer or neoplastic agent would provide the claimed effect, thus rendering the effect of enhancing the efficacy of a drug for a cancer cell obvious. Applicant respectfully disagrees with the Examiner and submits that there is no conclusive evidence in the case studies of Falk *et al.* that would even support the assertion

that HA is an efficient molecule to treat cancer. No controls in the 40 case studies were done regarding cancer treatment to show a specific effect for HA. Moreover, Falk *et al.* explicitly teach that cancer may be effectively treated by including NSAIDs, vitamin C, and glucose uptake inhibitors, such as phloretin in compositions containing HA. Applicant submits the majority of case studies use these agents in compositions containing HA, and that no controls were performed to demonstrate that HA exerted any positive effect at all. Applicant submits that the only experiment including a control, which is not relevant in the instant case, was done in rats and compared the abscess size of rats administered antibiotic (gentamycin) with or without HA (col. 37, lines 29-39 and Fig. 1).

Regarding evidence supporting the fact HA has surprising and unexpected properties at higher molecular weights, which are not present in the “preferred” molecular weight HA taught by Falk *et al.*, Applicant wishes to inform the Examiner of a forthcoming 37 C.F.R. rule 1.132 Declaration by Dr. Tracy Brown, which clearly shows that high molecular weight HA, within the claimed ranges of the Applicant possess surprising and unexpected properties that are not present in “the preferred” range of molecular weights described by Falk *et al.*

The skilled artisan, upon reading the Declaration provided by Dr. Tracy Brown, and examining the disclosure of Falk *et al.*, would have no choice to conclude that the surprising properties associated with the use of high molecular weight HA in combination with non-polynucleic acid-based cytotoxic or anti-neoplastic agent, namely increased drug efficacy and the properties of overcoming previously established drug resistance, were neither inherently or explicitly contained in the compositions of Falk *et al.* Thus, Falk *et al.* would not render the presently claimed methods obvious.

Accordingly, in light of the above amendments and remarks, Applicant kindly asks the Examiner to reconsider and withdraw these bases for rejection.

Rejection under 35 U.S.C. §102(b)/§103(a), second rejection

Claims 10, and 11 stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as obvious over Turley *et al.* (U.S. 6,475,795). Specifically, the Examiner contends that Turley *et al.* disclose anti-sense nucleic acid bound to HA for the purpose of treating diseases amenable to gene therapy. Further, the

Examiner contends that Turley *et al.* describe the use of high molecular weight HA in the range of 150-1000kD, and as such, anticipates the presently claimed methods. Applicant notes that claims 10-26 have been canceled, and thus, the Examiner's rejection is rendered moot with regard to claims 10, 11. However, Applicant will respond in full to the Examiner's arguments.

Applicant respectfully traverses these bases for rejection and submits that Turley *et al.* does not describe or suggest each and every limitation of the present claims, and thus, does not anticipate or render the presently claimed methods obvious. Moreover, Applicant questions the relevance of citing gene therapy methods to anticipate the presently claimed methods, which are clearly not methods of gene therapy.

Applicants submit that the present claims recite a non-polynucleic acid-based cytotoxic or anti-neoplastic agent. Thus, as Turley *et al.* is directed to the use of nucleic acid-based agents, this reference does not anticipate the present claims. Importantly, Turley *et al.* at no time describe or suggest the use of HA with non-polynucleic acid based agent. Furthermore, Turley *et al.* disclose HA as a delivery vehicle for these nucleic acids and fails to contemplate the use of high molecular weight HA to increase the efficacy of a drug, or alternatively, to use HA to overcome acquired drug resistance in a cancer cell.

Thus, the skilled artisan would not find it obvious upon reading Turley *et al.* to create methods that use non-polynucleic acid-based cytotoxic or an anti-neoplastic agents in combination with HA, as Turley *et al.* teach the use of nucleic acid-based therapeutics in order to obviate the inadequacies associated with current gene therapy protocols, namely efficient targeting and uptake of the therapeutic (col. 2, lines 22-25).

Accordingly, in light of the above amendments and remarks, Applicant kindly asks the Examiner to reconsider and withdraw these bases for rejection.

Rejection under 35 U.S.C. §103(a), first rejection

Claims 10, 12-14, 17, 19-22 and 24-26 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Falk *et al.* (U.S. 5,985,850). Specifically, the Examiner contends that Falk *et al.* administer the same composition of HA and drug as claimed in the Applicant's method, and thus, through inherency, the composition of Falk *et al.* would render the

presently claimed methods obvious. Applicant notes that claims 10-26 have been canceled, and thus, the Examiner's rejection is rendered moot with regard to claims 10, 12-14, 17, 19-22 and 24-26. However, Applicant will respond in full to the Examiner's arguments.

Applicant respectfully traverses this basis of rejection and submits that the surprising and unexpected results obtained through the administration non-polynucleic acid-based cytotoxic or anti-neoplastic agents with high molecular weight HA to cancer cells renders the presently claimed methods unobvious over Falk *et al.* Applicant refers the Examiner to the comments made in the previous §102(c)/§103(a) above and to the forthcoming declaration by Dr. Brown. Falk *et al.* fail to show efficacy of HA, fail to uncover surprising and unexpected properties associated with co-administration of agents with high molecular weight HA, and fail to propose the use of high molecular weight HA in combination with non-polynucleic acid-based cytotoxic or anti-neoplastic agents in order to accomplish the presently claimed methods of Applicant.

The Examiner alleges that Applicant's claimed ranges (750kD or 890kD, in previous Action) of molecular weights demonstrate surprising and unexpected results over the preferred ranges described in Falk *et al.* Applicant respectfully points the Examiner to the accompanying declaration supplied by Dr. Tracy Brown, which clearly demonstrates that HA within the preferred ranges of Falk *et al.* do not display the surprising and unexpected properties of the presently claimed molecular weight ranges for HA

Further, the Examiner contends that Falk *et al.* teach that HA with molecular weights greater than 750kD have effects on the clinical symptoms of pain and swelling. Applicant submits that the ranges described in Falk *et al.* to treat joint pain and inflammation with HA are from 1.2 megaDaltons to 7 megaDaltons. Applicant respectfully submits this is substantially higher than the amount of HA claimed in the present methods, and thus, is not relevant here. Furthermore, Applicant submits Falk *et al.*'s postulated use of HA to facilitate the transport of "agents" to tissues necessarily requires a lower viscosity HA (i.e., HA of low molecular weight). The skilled artisan would appreciate that the viscosity of HA is inherently determined by its molecular weight.

Further, the Examiner contends that one of the goals of Falk *et al.* is to provide formulations and conditions for delivery of medical and therapeutic agents for the treatment of diseases such as cancer. Applicant agrees, but also notes that in regard to HA, Falk *et al.* only consider its potential as a carrier, while postulating that compositions comprising NSAIDS, phloretin, and vitamin C are the molecules that actually affect the cancer cells. Moreover, as stated above, Falk *et al.* does not contain any conclusive evidence that HA is an effective or necessary molecule to use in combating cancer.

Applicant agrees with the Examiner, in that the skilled artisan would be motivated to look for the appropriate molecular weight HA to administer with non-polynucleic acid-based cytotoxic or anti-neoplastic agents in order to accomplish the presently claimed methods of Applicant. However, Applicant submits that the skilled artisan clearly recognizes that Falk *et al.*'s preferred molecular weight of HA (150-225kD) possesses much less viscosity than Applicant's claimed molecular weights for HA and not possess the surprising and unexpected properties imparted to higher molecular weight HA. Therefore, the artisan would not seek to use the compositions of Falk *et al.* to accomplish Applicant's methods of enhancing the efficacy of non-polynucleic acid-based cytotoxic or anti-neoplastic agents or overcoming the acquired resistance of a non-polynucleic acid-based cytotoxic or anti-neoplastic agent, as these properties are surprisingly and unexpectedly confined to high molecular weight HA, and thus, not inherently or expressly present in the compositions of Falk *et al.*

Applicant submits that Falk *et al.* fails to establish a *prima facie* case of obviousness against the claimed methods because the reference does not teach every limitation of the claims as discussed in the §102(e)/§103(a) rejection, comments above, and the forthcoming declaration. Moreover, the skilled artisan recognizes that the high molecular weight HA necessary to accomplish the claimed methods is not described or suggested by Falk *et al.*, as the methods therein seek to use low viscosity, high mobility HA. Applicant submits the skilled artisan recognizes that the low molecular weight HA of Falk *et al.* would accomplish the goal of using HA to transport molecules rather than effect drug treatment (Falk *et al.*'s own postulate), whereas the Applicant's high molecular weight HA inherently possesses different properties

such as increasing the efficacy of drug treatment against cancer cells and overcoming the acquired drug resistance of cancer cells.

Accordingly, as Falk *et al.* fail to establish a *prima facie* case of obviousness, Applicant kindly requests that the Examiner reconsider and withdraw this basis of rejection.

Rejection under 35 U.S.C. §103(a), second rejection

Claims 10, 11, 18, 20, and 23 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Falk *et al.* (U.S. 5,985,850) in view of Broder *et al.* (U.S. 5,968,972). Applicant notes that claims 10-26 have been canceled, and thus, the Examiner's rejection is rendered moot with regard to claims 10, 11, 18, 20, and 23. However, Applicant will respond in full to the Examiner's arguments.

Applicant respectfully traverses this basis of rejection and submits that based on the comments regarding the §102(e) and §103(a) rejections above, Falk *et al.* do not establish a *prima facie* case of obviousness against the presently claimed methods because they do not describe or suggest each and every limitation of the claims. Moreover, as Broder *et al.* merely teach increasing the bioavailability of the anti-neoplastic agent paclitaxel, this reference cannot cure the insufficiencies of Falk *et al.*, and thus, neither reference alone or in combination establishes a *prima facie* case of obviousness against the presently claimed invention.

Accordingly, in light of the above amendments and remarks, Applicant kindly asks the Examiner to reconsider and withdraw these bases for rejection.

Rejection under 35 U.S.C. §103(a), third rejection

Claims 10-26 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Turley *et al.* (U.S. 6,475,795) in view of Buckbinder *et al.* (U.S. 5,840,673) or Johnson *et al.* (U.S. 6,087,350). Specifically, the Examiner contends that Turley *et al.* disclose anti-sense nucleic acid bound to HA for the purpose of treating diseases amenable to gene therapy. Further, the Examiner contends that Turley *et al.* describe the use of high molecular weight HA in the range of 150-1000kD, and as such, anticipates the presently claimed methods.

Further the Examiner contends that Buckbinder *et al.* and Johnson *et al.* recognize paclitaxel, methotrexate, 5-FU, cisplatin, cyclophosphamide, and camptothecin. Further, the Examiner contends that the skilled artisan would find it obvious to substitute the cytotoxic agents of Buckbinder *et al.* and Johnson *et al.* for the nucleic acid conjugated to HA in order to arrive at the presently claimed invention. Applicant notes that claims 10-26 have been canceled, and thus, the Examiner's rejection is rendered moot with regard to claims 10-26. However, Applicant will respond in full to the Examiner's arguments.

Applicant respectfully traverses these bases for rejection and submits that Turley *et al.* does not describe or suggest each and every limitation of the present claims, and thus, does establish a *prima facie* case of obviousness. Moreover, the skilled artisan would not find it obvious to substitute non-nucleic acid based cytotoxic agents for the nucleic acid based agents of Turley *et al.*, and thus, neither reference alone or in combination establishes a *prima facie* case of obviousness against the presently claimed methods. Furthermore, as discussed in the §102(b) rejection, Turley *et al.* disclose HA as a delivery vehicle for these nucleic acids and fails to contemplate the use of high molecular weight HA to increase the efficacy of a drug, or alternatively, to use HA to overcome acquired drug resistance in a cancer cell. Significantly, Turley *et al.* at no time describe or suggest the use of HA with non-polynucleic acid based agents. Applicant reiterates the questionable relevance of gene therapy methods to the presently claimed methods, which are clearly not methods of gene therapy.

Applicant submits that Turley *et al.* teach polynucleic acid-based cytotoxic agents conjugated to HA for use in gene therapy. A skilled artisan would not find it obvious to substitute drugs for nucleic acid based molecules in gene therapy, as **gene therapy necessarily requires genetic material**. Applicant submits that perhaps modified nucleic acid molecules would be acceptable replacements, but the skilled artisan would not substitute cytotoxic drugs, which have different modes of action, different toxicity considerations, different delivery considerations etc. Applicant submits that the Examiner is engaging in the impermissible use of hindsight in order to argue a *prima facie* case of obviousness against the claimed methods. Applicant maintains that there is no commonality between the groups of references other than they use cytotoxic agents to treat cancer (*i.e.*, defining the problem in terms of its solution). By

the Examiner's line of reasoning, one could simply identify any references that recite cytotoxic agents in the treatment of cancer and substitute them, regardless of their context, for the nucleic acids in Turley *et al.* Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness. *Monarch Knitting Machinery Corp. v. Sulzer Morat GMBH*, 139 F.3d 877, 811, 45 U.S.P.Q.2d 1977 (Fed. Cir.1998). Applicant submits that it is solely the Applicant's finding that combining non- polynucleic acid-based cytotoxic or an anti-neoplastic agents in combination with HA yields an increase the efficacy of a drug, or alternatively, to use HA to overcome acquired drug resistance in a cancer cell.

Applicant submits that the skilled artisan would not find the claimed methods obvious over Turley *et al.* in view of Buckbinder *et al.* or Johnson *et al.*, and thus, these references fail to establish a prima facie case of obviousness. The skilled artisan would not seek to combine the references cited by the Examiner, because they employ vastly different technologies, although each category of molecule is a cytotoxic agent.

Accordingly, in light of the above amendments and remarks, Applicant kindly asks the Examiner to reconsider and withdraw these bases for rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now clearly allowable.
Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,
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